**Title**: Neurodevelopmental features among infants with benign congenital hypotonia in high southern latitudes: An observational cross-sectional trial.

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## Abstract

**Objective**: To describe and model the relationship between sociodemographics, prematurity and neurodevelopmental levels based on the *Ages and Stages Questionnaire* scores in infants diagnosed with benign congenital hypotonia (BCH). **Material and methods**: […]. **Results**: […]. **Conclusion**: After adjusting for possible confounders, we found between-subjects fluctuations in neurodevelopmental traits across age in hypotonic infants in the form of non-linear and domain-specific variations. Further research is warranted to determine how these findings apply in the presence of other context-mediated social factors and populations.

**Keywords**: […].

# Introduction

Both physical and psychological signs of early childhood development have been shown to be representative and relevant markers for the identification and monitoring of overall growth in early life ([Di Rosa et al., 2016](#ref-di2016predictive)) and can, therefore, be used in the screening of children at risk of developmental delay to support early referral and need further assessment to determine if they are eligible for early intervention services ([Bruder, 2010](#ref-bruder2010early); [Guralnick, 2017](#ref-guralnick2017early)).

Currently, a plethora of tools have been proposed to assess the developmental continuum of infants. In this sense, the Ages and Stages Questionnaire, Third Edition (ASQ-3) has been proposed as a global screening tool, parent/caregivers-oriented, that assesses five domains of development in children aged from 0 to 5.5 years old ([Singh, Yeh, & Blanchard, 2017](#ref-singh2017ages)). Current evidence suggests that the ASQ-3 is an accurate, cost-effective yet parent-friendly instrument for screening, monitoring children up to pre-school age, and can help identify and exclude neurodevelopmental impairments in very preterm-born children ([Ballantyne, Benzies, McDonald, Magill-Evans, & Tough, 2016](#ref-ballantyne2016risk); [Kerstjens et al., 2015](#ref-kerstjens2015ages); [Singh et al., 2017](#ref-singh2017ages)).

Hypotonia has been defined both as decreased muscle tone or floppiness, involving a wide range and levels of progression ([Gabis et al., 2021](#ref-gabis2021weak); [Harris, 2008](#ref-harris2008congenital)). There are multiple forms of neuromuscular, metabolic and genetic conditions associated with hypotonia and it may be a sign of neurodevelopmental delay, that may predispose to cognitive impairment ([Riou, Ghosh, Francoeur, & Shevell, 2009](#ref-riou2009global)). Given that hypotonia, and the hyperlaxity and motor delay associated with it, may impair the infant’s capacity to engage with its surroundings, critical visual cues may be ignored, potentially leading both to an impairment of learning and cognitive development ([Harris, 2008](#ref-harris2008congenital)), hence the need to explore the neurodevelopmental attributes of infants with hypotonia.

Accordingly, benign congenital hypotonia (BCH) is usually considered an exclusion diagnosis, and is usually made in the absence of other signs and symptoms, after every other evaluative resources have been exhausted ([Gabis et al., 2021](#ref-gabis2021weak); [Leyenaar, Camfield, & Camfield, 2005](#ref-leyenaar2005schematic)), however this is not true for at least one author that suggest that BCH can not be considered a diagnosis as such ([Thompson, 2002](#ref-thompson2002benign)). BCH is considered a non-progressive neuromuscular disorder that does not progress but tends to improve with time and early intervention.

Nevertheless, and to the best of our knowledge, there is no robust evidence characterising the observed variation in developmental traits in infants with known BCH across age. Therefore, our main objective in this study was to describe and model the relationship between sociodemographics, prematurity and neurodevelopmental levels based on ASQ-3 scores in infants with diagnosed BCH.

# Material y methods

## Study design

We conducted an observational, cross-sectional study, under a quantitative approach.

¿Los datos vienen de algún grupo de estudio o de cohorte en particular?

¿Qué resguardos éticos se consideran? Comité de ética y otros permisos que sean pertinentes

## Participants

¿Cómo fueron reclutados los sujetos? Criterios de elegibilidad, tipo de muestreo, etc.

¿Cómo, cuando y quien hizo el diagnóstico de hipotonía congénita?

## Measures

### The Ages and Stages Questionnaire, third edition (ASQ-3)

The ASQ-3 is a parent reported initial level developmental screening instrument consisting of 21 intervals, each with 30 items in five areas: i) communication (CM), ii) gross motor (GM), iii) fine motor (FM), iv) problem-solving (CG), and v) personal-social (PS). The ASQ is cost-effective and widely used in the United States and other countries. The ASQ has been translated into several languages, and the number of international studies on its psychometric properties with diverse cultural environments is increasing. It has excellent psychometric properties, test-retest reliability of 92%, sensitivity of 87.4% and specificity of 95.7%. Its validity has been examined across different cultures and communities across the world.

## Procedures

### Collection of demographic data

¿Como, cuando y quién recolectó los datos demográficos?

### Assessment with ASQ-3

¿Cómo se evaluó el ASQ-3? ¿Con qué protocolo? ¿Que consideraciones se tuvieron en la evaluación? ¿Algo más que podría ser relevante para agregar respecto a la evaluación o corrección del cuestionario?

## Statistical analysis

Data is presented as median (*Mdn*) and interquartile range (*IQR*) for continuous variables; for categorical/discrete variables, the absolute and relative sample size was reported.

A non-parametric approach was used since the underlying distribution of continuous measured outcomes, assessed through analytical and graphical methods, did not follow a Gaussian distribution.

In order assess the differences in developmental scores between males and females, the *Wilcoxon* rank-sum test was used, meanwhile the chi-square test () was used to evaluate goodness-of-fit () and independence of factors ().

Generalized additive models (GAM) were used to describe linear and non-linear relationships in the form of smooth terms between developmental characteristics, represented through penalized regression splines ([Wood, 2011](#ref-wood2011fast)). Restricted maximum likelihood method was used for the estimation of the smoothing parameters, and thin-plate regression splines as the smoothing basis, as they are the optimal smoother of any given basis dimension/rank ([Wood, 2003](#ref-wood2003thin)). In the final models, infants’ sex, clinician and infants’ relationship with caregivers were added as random effects in the form of penalized parametric terms to account for the variability arising from these variables in the fixed effects analysed ([Wood, N., Pya, & S"afken, 2016](#ref-wood2016smoothing)). To describe the smooth terms by means of quasi-linear segments, we used approximative derivatives with 95% confidence intervals (CI95%).

A probability of committing a type I () error of less than 5% (*p* < 0.05), was considered sufficient evidence for statistical significance in hypothesis testing. All the statistical analyses were computed and implemented in the R programming language ([R Core Team, 2021](#ref-rlanguage)). GAMs and the corresponding model estimates were computed using the *mgcv* and *modelbased* packages, each with well documented functions and methods ([Makowski, Ben-Shachar, Patil, & Lüdecke, 2020](#ref-dominique2020estimation); [Wood, 2017](#ref-wood2017generalized)). Complementary R packages were used for visualization purposes ([Lüdecke et al., 2021](#ref-daniel2021see); [Wickham, 2016](#ref-hadley2016ggplot2)).

# Results

From a total of 234 subjects with congenital hypotonia, 94 (40.2%) were females and 140 (59.8%) males ( (1) = 9.04, *p* = 0.003, = 0.19, CI0.95%[0.09, 1]). The developmental characteristics of the sample can be seen in [Table 1](#tab1).

When modelling the effect of chronological age on developmental domains, corrected for prematurity, we observed a significant non-linear relationship on CM scores ( (5.2, 224.04) = 13.43, *p* < 0.001), that reflect an overall negative marginal effect ( = -2.36, CI95%[-3.47, -1.25], (224.04) = -4.2, *p* < 0.001), however, this was not true when assessing the direction of the effect in the age range between 0 to 6.8 ( = 0.49, CI95%[-0.89, 1.86], (224.04) = 0.45, *p* = 0.319), neither in the 18.4 to 48 months old group ( = 0.45, CI95%[-1.32, 2.23], (224.04) = 0.42, *p* = 0.593), whereas the effect tend to be positive but non-significant. The relationship between developmental domains, corrected age and their effect derivatives can be seen in [Figure 1](#fig1).

When analysing the motor skills domain, we found a significant non-linear effect of corrected age on GM scores, (5.24, 226.75) = 6.19, *p* < 0.001, which had an overall positive effect ( = 1.95, CI95%[0.66, 3.25], (226.75) = 2.97, *p* = 0.003), however, the slope varied as a function of age, with a negative effect in the 0 to 6.8 age range ( = -2.94, CI95%[-4.55, -1.34], (226.75) = -3.7, *p* = 0.004), but in the 9.7 to 15.5 interval, this relationship was inverted ( = 1.86, CI95%[0.61, 3.11], (226.75) = 2.93, *p* = 0.009), however, in the rest of the age range the slope was non-significant and virtually zero (Age[7.3, 9.2], = 0.02, CI95%[-1.12, 1.17], (226.75) = 0.06, *p* = 0.45; Age[16, 48], = -0.02, CI95%[-2.05, 2.01], (226.75) = 0.07, *p* = 0.646).

Despite the fact that a similar non-linear effect was observed when inspecting the influence of corrected age in the FM domain scores ( (2.59, 226.77) = 4.2, *p* = 0.005), it was not possible to estimate a significant overall effect different from zero ( = 0.04, CI95%[-0.45, 0.52], (226.77) = 0.14, *p* = 0.886), nevertheless, it was only in the 22.3 to 38.3 age range where a significant and negative effect was observed ( = -0.79, CI95%[-1.45, -0.12], (226.77) = -2.34, *p* = 0.022).

CG abilities were significantly influenced by corrected age ( (5.66, 227.01) = 3.65, *p* = 0.001), with an overall negative effect ( = -1.87, CI95%[-3.17, -0.57], (227.01) = -2.83, *p* = 0.005), and just like the other domains, this relationship was modified across corrected age. In this sense, from the 0 to 5.8 age interval, we found that for every increase in one month in corrected age, we can expect a proportional increase in 2.81 points ( = 2.81, CI95%[1.18, 4.44], (227.01) = 3.49, *p* = 0.002) in the CG domain, while in the age range 9.2 to 14.1 the relationship changes inversely, mainly because in this age range we observe that for every one-month increase in the corrected age, a decrease of 1.59 points could be expected in the same domain ( = -1.59, CI95%[-2.82, -0.37], (227.01) = -2.55, *p* = 0.015). The other age intervals did not have a slope that deviated significantly from zero (Age[6.3, 8.7], = 0.05, CI95%[-1.1, 1.2], (227.01) = 0.06, *p* = 0.395; Age[14.5, 48.0], = 0.03, CI95%[-1.99, 2.04], (227.01) = -0.06, *p* = 0.55).

Unlike the others, PS domain was not influenced by corrected age ( (1, 231.58) = 1.16, *p* = 0.282). Accordingly, prematurity (measured in weeks) was not associated with any developmental domain within ASQ-3 assessment (significance for smooth terms: CM, *p* = 0.715; FM, *p* = 0.987; GM, *p* = 0.357; CG, *p* = 0.292; PS, *p* = 0.131).

# Discussion

Our study aimed to describe and model the relationship between sociodemographic data, prematurity and neurodevelopmental levels based on ASQ-3 scores in infants diagnosed with BCH. Our main findings suggest a non-linear effect of age, corrected for prematurity, with a marked decrease in scores for all neurodevelopmental traits at different age frames, even after adjusting for caregiver relationship, sex and inter-rater influence. However in the personal-individual domain, there was no variation observed across corrected age.

This could be associated with the described motor impairments of hypotonia in the early stages of life, which could compromise the infant’s ability to explore and interact with his or her environment ([Gabis et al., 2021](#ref-gabis2021weak); [Harris, 2008](#ref-harris2008congenital)). A reflection of the aforementioned would be expressed in an altered development of GM function in the first months of life, with a consequent limitation in FM skills later on, which would have a subsequent negative impact on the communicative competence of infants, secondary to a reduced interaction with their environment and peers. The results found in our study are congruent with what other authors have discussed in relation to the role of gross and FM skills in language development ([Gonzalez, Alvarez, & Nelson, 2019](#ref-gonzalez2019gross)).

It is worth noting that other context-mediated social factors may also have influenced our results, mainly due to the role that other variables would also play in the neurodevelopment of our study sample, which could have an impact on many of the developmental traits assessed here, such as intrauterine growth restrictions, maternal depression, institutionalisation, exposure to social violence, maternal education and breastfeeding ([Walker et al., 2011](#ref-walker2011inequality)). All together, these represent the main limitations in our study design, which need to be addressed in future research exploring the variations observed in different developmental traits in hypotonic infants. However, our study sheds light to an underexplored aspect of congenital myopathies, with robust statistical methods that made it possible to model and capture the complex relationships seen early in life.

# Conclusion

The present study shows that the marked variations observed in neurodevelopmental traits are present across age in hypotonic infants, mainly in the form of non-linear and domain-specific variations, even after adjusting for the effect that caregiver relationship, gender and evaluators might exert. Moreover, we show that the observed variations in developmental domains are not solely attributable to prematurity, where age corrected for prematurity best explained the observed variability in neurodevelopment. Further research is warranted to determine how these findings apply when controlling for context-mediated social factors and in other populations.

# Acknowledgment

[…].

# Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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**Table 1**. Overall baseline and developmental characteristics of the sample and grouped by sex. 1 Data is presented as sample size, and *Mdn* (*IQR*); 2 p-values are computed from the *Wilcoxon* rank-sum test.

**Figure 1**. Relationship between corrected age (in months) and developmental domains. Left panel: regression lines and shaded area represent predicted values estimated from GAM models and their CI95%, points and error bars represent the mean and standard error at 5-month age intervals. Right panel: effect derivatives representing how the effect of corrected age (in months) in developmental domains changes across corrected age. Significant areas consider CI95% that did not cross zero.